REMARKS

Applicants thank Examiner Housel for the helpful in-person interview with Dr. Lee Mizzen, Len Rasile, and the undersigned on August 26, 2003.

Claims 1-4, 6, 8-13, and 36-83 are pending in the application. Claims 1-4, 6, 40-43, 54-57, and 68-71 have been amended. Claims 81-83 have been added by the present amendment. Support for these amendments and new claims can be found in the specification at, e.g., page 1, lines 2-18; page 2, line 20, to page 4, line 9; and page 8, lines 24-27. These amendments add no new matter.

Improper Finality of Office Second Action

On page 13 of the Office Action, the Examiner asserted that applicants' amendment in response to the first Office Action necessitated the new grounds of rejection. For this reason, the Examiner made final the present second Office Action.

Applicants respectfully submit that the amendments made in response to the first Office Action did not necessitate all new grounds of rejection. For example, the Examiner put forth in the second Office Action a new rejection under 35 USC § 102(f), based upon information contained in the present specification and in Mizzen et al., WO 99/07860. However, no claim amendment made in the response to the first Office Action necessitated the Examiner's new assertion under 102(f) that applicants are not the true inventors of the claimed invention. Similarly, nothing in the new rejection over Mizzen et al., U.S. Patent No. 6,524,825 (which is the U.S. national phase of WO 99/07860, and thus has the same specification as WO 99/07860) is related to a claim amendment made in response to the first Office Action.

A second Office Action on the merits cannot be made final if it introduces a new ground of rejection that is neither necessitated by applicants' amendments of the claims nor based on information submitted in an Information Disclosure Statement. See MPEP § 706.07(a). This restriction on the imposition of finality protects an applicant from the unfair position of facing a final rejection on an issue of first impression for a matter where applicant has taken no action (e.g., making a claim amendment or submitting an Information Disclosure Statement) that

justifies such a hardship. Because at least one of the new grounds of rejections in the present Final Office Action was not necessitated by an amendment to the claims, applicants request that the Examiner withdraw the finality of the Office Action.

Anticipation Rejections

The Examiner rejected the claims as allegedly anticipated by several different references, as detailed below. These rejections and the types of responses by applicants that could potentially overcome such rejections were discussed extensively during the in-person interview with Examiner James Housel held on August 26, 2003. The following comments apply to all of the rejections, since for each rejection the Examiner made the identical assertion that "while the Applicants may have "Observed" something interesting they have not have [invented] anything new."

Contrary to the Examiner's assertions, the claimed invention is much more than a mere observation. As detailed in the working examples contained in the application as filed, applicants made the surprising discovery that a fusion protein containing an Hsp60 protein and an HPV type 16 E7 antigen was effective in treating warts in patients that tested negative for HPV type 16 but tested positive for other HPV types, such as HPV types 6 and 11. This observation was made during the course of a clinical trial using HspE7 (a fusion protein containing M. bovis BCG Hsp65 and HPV type 16 E7) to treat patients having a condition (anal high grade squamous intraepithelial lesions (HSIL)) primarily caused by HPV type 16. A subset of the patients participating in the trial also had a second, different condition (genital warts). During the course of the trial, it was discovered that some of those patients that had genital warts but tested negative for HPV type 16 showed an improvement in this second condition (see specification at page 18, line 23, to page 24, line 16). Both in this clinical trial and in the population at large, these first and second conditions occur in non-coextensive groups of individuals. A given individual can have (i) anal HSIL but not genital warts, (ii) genital warts but not anal HSIL, (iii) anal HSIL and genital warts, or (iv) neither anal HSIL nor genital warts.

In the present patent application, applicants have applied their surprising discovery described above to claim a method of using an Hsp-HPV fusion protein to treat a particular group of subjects that is divergent from the subjects treated with an Hsp-HPV fusion protein in the cited references. The claims require that the subject being treated have a wart that is caused by an HPV type that differs from the HPV type from which the HPV E7 protein or antigenic fragment thereof contained in the fusion protein is derived.

To anticipate a claim, a prior art reference must disclose every feature of the claim, either explicitly or inherently. *Hazani v. U.S. Int'l Trade Comm'n*, 126 F.3d 1473, 1477 (Fed. Cir. 1997). "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1297 (Fed. Cir. 2002). "A reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations." *Eli Lilly & Co. v. Barr Laboratories, Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001).

The cited references describe the treatment of a variety of conditions caused by HPV infection. However, none of the cited references describes using an HPV E7 protein or an antigenic fragment thereof of a first HPV type to treat a wart caused by a second HPV type. Furthermore, none of the treatment methods of the cited references necessarily encompasses treating a wart in a subject that is caused by a type of HPV that differs from the type of HPV E7 protein or antigenic fragment thereof administered to the subject in the fusion protein. That a subject would also have such a second, different condition (i.e., in addition to the first condition described in the reference) is clearly not a natural result that flows from a subject having the first condition. Because the claimed methods are directed to the treatment of subject populations that are divergent from those treated by the methods of the cited references, none of the references anticipates the claimed invention.

The Examiner cited *In re Cruciferous Sprout Litigation*, 64 USPQ2d 1202 (Fed. Cir. 2002) in support of the each of the anticipation rejections. In *Cruciferous*, the applicant Brassica had merely recognized properties that were inherent in certain prior art

sprouts, but had failed to claim a new sprout or a new way of growing sprouts. It was for this reason that the Court concluded that Brassica's claims were inherently anticipated. In contrast to *Cruciferous*, applicants have not recognized the mechanism by which a prior art method works. Instead, applicants have discovered a new way of treating disease and have applied that discovery to present method claims that are disclosed neither explicitly nor inherently in the prior art.

The specific rejections are addressed in detail below.

Mizzen et al. (35 U.S.C. § 102(b) and 102(e))

On pages 6-7 of the Office Action, the Examiner rejected claims 1-4, 6, 8-13, and 36-80 as allegedly anticipated by Mizzen et al., WO 99/07860 ("Mizzen"). In addition, on pages 11-12 of the Office Action, the Examiner rejected the claims as allegedly anticipated by Mizzen et al., U.S. Patent No. 6,524,825. Because these two references contain the same disclosure (the U.S. patent is the U.S. national phase of the PCT application), applicants address both references in the following comments.

Claim 1 is directed to a method of treating a wart in a subject by administering a fusion protein containing an Hsp60 protein (or an immunostimulatory fragment thereof) and an HPV E7 protein (or an antigenic fragment thereof). The claim also specifies that the wart is caused by an infection with an HPV type that differs from the HPV type from which the HPV antigen was derived.

Mizzen discloses the use of an Hsp-HPV fusion protein to treat tumor cells expressing HPV E6 and E7 proteins. However, Mizzen does not disclose using an E7 protein from one type of HPV to induce a cross reactive immune response to treat a wart caused by a second type of HPV. For example, the working examples of Mizzen disclose the prophylactic and therapeutic use of HspE7 (a fusion protein containing M. bovis BCG Hsp65 and HPV type 16 E7) in a mouse model of cervical cancer wherein a tumor cell line (TC-1) transformed with HPV type 16 E6 and E7 genes is injected subcutaneously into a mouse. The examples of Mizzen thus use a fusion protein containing an HPV type 16 protein to induce an immune response against a tumor

expressing an HPV type 16 protein. This is an HPV type-specific immune response. Mizzen nowhere describes using a fusion protein containing a protein antigen of one HPV type to treat a wart caused by an infection with a second HPV type. The Examiner has pointed to no particular passage of Mizzen that even allegedly discloses a treatment method that anticipates the claimed treatment method. Furthermore, because Mizzen discloses the treatment of subject populations that are divergent from those treated by the claimed methods, the reference does not inherently anticipate the claimed invention. Accordingly, applicants request that the Examiner withdraw the rejection.

Chu et al. (35 U.S.C. § 102(b))

On pages 7-8 of the Office Action, the Examiner rejected claims 1-4, 6, 8-13, and 36-80 as allegedly anticipated by Chu et al. (1998) FASEB J. 12(5):A909 ("Chu").

Chu discloses the use of HspE7 (a fusion protein containing an M. bovis BCG Hsp65 protein and HPV 16 E7) in a mouse tumor rejection system that is a model for cervical cancer. In the mouse tumor system, as detailed above in the comments regarding the Mizzen reference, the HPV type 16 E6/E7 transformed tumor cell line TC-1 was injected subcutaneously into mice. Prophylactic immunization with HspE7 (i.e., a composition containing HPV type 16 E7) provided protection to mice that were later challenged with the tumor cell line. In addition, HspE7 treatment of mice carrying the TC-1 tumor resulted in tumor regression.

Chu does not describe a method of treatment that uses a fusion protein containing an HPV E7 protein antigen of one HPV type to treat a wart caused by an infection with a second HPV type. Rather, Chu describes using a fusion protein containing an HPV type 16 antigen to induce a type-specific immune response against a tumor expressing HPV type 16 antigens. Furthermore, Chu describes the treatment of a subject population that is divergent from the subjects treated by the claimed methods. Accordingly, Chu does not inherently anticipate the claimed invention. Applicants request that the Examiner withdraw the rejection.

Zhou (35 U.S.C. § 102(a))

On pages 8-9 of the Office Action, the Examiner rejected claims 1-4, 6, 8-13, and 36-80 as allegedly anticipated by Zhou, CN1248631A. An English language translation of the entire patent application of Zhou is enclosed with the present response.

As detailed herein, claim 1 is directed to a method of treating a wart in a subject by administering to the subject a fusion protein containing an Hsp60 protein (or an immunostimulatory fragment thereof) and an HPV E7 protein (or an antigenic fragment thereof), wherein the wart is caused by an infection with an HPV type that differs from the HPV type of the E7 protein (or an antigenic fragment thereof) contained in the fusion protein.

Zhou describes a fusion protein containing an M. bovis BCG heat shock protein fused to an HPV protein. Zhou states that the fusion protein can be used as an immunogen in prophylactic and therapeutic applications. However, Zhou does not indicate that the fusion protein can be used to induce a cross reactive immune response to treat a wart caused by an HPV type that differs from the HPV type from which the HPV antigen in the fusion protein was derived. In fact, Zhou clearly states that the fusion protein described therein induces an immune response that is HPV type-specific (see Zhou at the bottom of page 3 stating that the fusion protein containing an HPV type 16 E7 protein induced cellular and humoral immune responses that "are specific to HPV-16-E7"). Because Zhou describes the induction of a type-specific immune response, Zhou's description of the use of an HPV type 16 E7-containing fusion protein to treat or prevent acute condyloma and tumors is necessarily understood to refer to acute condyloma and tumors caused by HPV type 16. As detailed in Exhibits A[1] and B[2] enclosed with the present response, HPV type 16 infection is associated with both malignant genital lesions as well as acute condyloma (also termed "condyloma acuminata" or "genital warts").

Zhou does not describe treating a wart by administering to a subject a fusion protein containing an HPV E7 protein of one HPV type to treat a wart caused by an infection with a second HPV type. As detailed above, Zhou describes only the induction of type-specific anti-HPV immune responses. Furthermore, because Zhou discloses the treatment of subject

[1] Brown et al. (1993) J. Clin. Microbiol. 31(10):2667-73.
[2] Beckmann et al. (1991) J. Infect. Dis. 163(2):393-96.

populations that are divergent from those treated by the claimed methods, the reference does not inherently anticipate the claimed invention. Accordingly, applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 102(f)

On pages 12-13 of the Office Action, the Examiner rejected claims 1-4, 6, 8-13, and 36-80 on the basis that applicants allegedly did not invent the claimed subject matter. In particular, the Examiner asserted that, instead of applicants, the true inventors of the present application are the ones named in Mizzen et al., WO 99/07860.

First, applicants note that Stressgen Biotechnologies Corporation, the assignee of WO 99/07860 (Mizzen et al., discussed *supra*), is also the assignee of the present application. Second, as detailed in the specification, applicants used the HspE7 fusion protein composition described and claimed in WO 99/07860 in a clinical trial for the treatment of anal high grade squamous intraepithelial lesions. During the course of that clinical trial, applicants discovered a new and unexpected use for the composition and now seek patent protection for that new use in the currently pending method claims. It is a fundamental principle that an individual can use a prior art composition and, upon finding a new use for that composition, the individual can properly secure a patent claim that covers a method of using the prior art composition. In the present case, applicants claim neither a composition nor a method described in WO 99/07860.

The Examiner has cited a passage from Goldstone et al. (2002) Dis. Colon Rectum 45:502-507 (an academic publication of the findings of the present application), noting that the results of the clinical trial were tabulated retrospectively rather than prospectively. The retrospective nature of this study merely underscores the fact that the effectiveness of the HspE7 composition in treating genital warts was an unexpected finding and that the applicants are the true inventors of the claimed invention.

In light of these comments, applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 112, 2nd Paragraph (Indefiniteness)

On pages 2-3 of the Office Action, the Examiner rejected claims 1-4, 6, 8-13, and 36-80 as allegedly indefinite in their recitation of the following phrases: "immunostimulatory fragment," "antigenic fragment," and "sufficient amount."

The claim term "immunostimulatory fragment" of an Hsp60 protein refers to a portion of an Hsp60 protein that, when contained in a fusion protein that also contains an HPV E7 protein or antigenic fragment thereof, facilitates an immune response to the HPV E7 protein or antigenic fragment thereof in a subject to whom the fusion protein is administered (see specification at page 4, line 29, to page 5, line 6). In addition, the claim term "antigenic fragment" of an HPV E7 protein refers to a portion of an HPV E7 protein that, when contained in a fusion protein that also contains Hsp60 protein or immunostimulatory fragment thereof, elicits, in a subject to whom the fusion protein is administered, an immune response against the HPV E7 protein or the HPV E7 protein fragment (see specification at page 4, lines 18-28).

The specification clearly defines the claim terms "immunostimulatory fragment" and "antigenic fragment" in the manner described above. As noted by the Examiner in the Office Action, claims are interpreted in light of the specification. Such recourse to the specification serves to assist in interpreting an applicant's meaning for a given claim term, *not* to read in limitations that are not already present in the claim. Such claim interpretation contrasts with *In re Van Geuns*, 988 F.2d 1181 (Fed. Cir. 1993), a case cited by the Examiner, wherein an applicant attempted to impermissibly read a limitation from the specification into a claim. In *Van Geuns*, the applicant had presented an argument concerning a limitation that, though described in the specification, was simply was not present in the claim. Accordingly, *Van Geuns* properly stands for the proposition that limitations are not to be read into the claims from the specification. In contrast to *Van Geuns*, the terms "immunostimulatory fragment" and "antigenic fragment" both appear in claim 1 and are thus limitations of the claim. Reference to the definitions of the terms provided in the specification merely serves to interpret the claim terms, not to read limitations from the specification into the claim.

Turning to the clarity of the claim terms, in view of the definitions as provided in the specification, the claimed methods encompass the use of a fusion protein that contains fragments that must have the structural properties (i.e., contain a portion of the amino acid sequence of an Hsp60 or an HPV E7 protein) and functional properties (i.e., be immunostimulatory or antigenic) recited in the claims. Because a person of ordinary skill in the biological arts would readily understand the meaning and scope of these claim terms and whether a given fusion protein falls within the scope of the claim, the metes and bounds of the claims are clear. Accordingly, the claims satisfy the definiteness requirement.

The Examiner asserted that the phrase "amount sufficient" renders claim 1 indefinite. The claim requires that the recited composition be administered to a subject "in an amount sufficient to treat the wart." It is standard practice that method of treatment claims in the field of biotechnology recite phrases such as "an effective amount" or "an amount sufficient" to indicate the amount of an active composition that must be administered to fall within the method. Furthermore, it is also standard practice that numerical dosages or dosage ranges are not recited in such claims. Such practice in the field of biotechnology is the result of the understanding that claim terms such as "effective" or "sufficient" have meanings that are abundantly clear to the skilled biologist. Applicants strongly contest the Examiner's assertion on page 3 of the Office Action that the claimed method must recite a range of amounts in order to be clear as to what constitutes a "sufficient" amount of the composition to be used in the claim. Because a person of ordinary skill in the biological arts understands that the "amount sufficient" to treat a wart may vary from subject to subject, and such a person would be able to readily recognize whether or not a given dosage was "sufficient" to treat a wart, the claim term is sufficiently definite. Accordingly, applicants request that the Examiner withdraw the rejection.

At page 10 of the Office Action, the Examiner rejected claim 1 as allegedly indefinite in its recitation of the phrase "Hsp60." The Examiner asserted that the intended metes and bounds of "Hsp60" is not defined and asked whether "Hsp60" is a trademark or made-up acronym.

"Hsp60" is neither a trademark nor an acronym made up by applicants. Rather, the term is one that is used standardly by biologists to refer to a heat shock protein ("Hsp") belonging to a particular Hsp family designated "Hsp60." As detailed in the specification, "Hsp60" includes proteins derived from organisms such as mycobacteria, bacteria, and eukaryotes (page 7, line 28; and page 8, lines 24-27). As confirmation that "Hsp60" is a term that has a standard and clear meaning to the skilled biologist, enclosed as Exhibit C[3] is a review article describing Hsp60 family members and summarizing features of Hsp60 proteins that were well known to the skilled artisan at the time of filing of the present application (see, e.g., Exhibit C at page 440 and pages 465-468). Hsp60 proteins constitute one of the major classes of Hsps and share a highly conserved amino acid sequence and structure that distinguishes them from other classes or families of Hsps. Based upon such designations, the skilled artisan would readily understand whether a given protein constitutes an "Hsp60" and falls within the claim limitations. Because the claim term "Hsp60" has a clear meaning to the skilled artisan, applicants respectfully request that the Examiner withdraw the rejection.

At page 10 of the Office Action, the Examiner rejected claim 1 as allegedly "incomplete for omitting essential elements, such omission amounting to a gap between the elements." According to the Examiner, the omitted "elements" are "the 'immunostimulatory fragment' which would be suited to treat HPV, the HPV E7 protein and its 'fragment."

The Examiner cited MPEP § 2172.01 in support of the present rejection. The first paragraph of § 2172.01 is concerned only with 35 U.S.C. 112, first paragraph, and thus does not apply to the present rejection under 35 U.S.C. 112, second paragraph. The second paragraph of § 2172.01 states that a "claim which fails to interrelate essential elements of the invention as defined by applicant(s) in the specification may be rejected under 35 U.S.C. 112, second paragraph, for failure to point out and distinctly claim the invention."

Applicants respectfully traverse the rejection. Independent claim 1 requires that the fusion protein used in the treatment method contain (1) an Hsp60 protein or an

---

[3] Parsell and Lindquist (1993) Annu. Rev. Genet. 27:437-96.

immunostimulatory fragment thereof, and (2) an HPV E7 protein or an antigenic fragment thereof. Claim 1 interrelates elements (1) and (2) by requiring that they both be present in the fusion protein that is administered to the subject. Because these elements of the composition used in the claimed method are clearly interrelated, claim 1 satisfied the definiteness requirement. Accordingly, applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 112, 1st Paragraph (Enablement)

On pages 3-5 of the Office Action, the Examiner rejected claims 1-4, 6, 8-13, and 36-80 as allegedly not enabled. According to the Examiner, it would require undue experimentation to practice the full scope of the claimed invention. In particular, the Examiner objected to the breadth of claim terms such as "Hsp60" and an "immunostimulatory fragment" of an Hsp60 protein as well as an "antigenic fragment" of an HPV E7 protein.

Applicants note that the Examiner acknowledged in the first Office Action that the specification is "enabling for a method of inducing [an] immune response utilizing Hsp65 heat shock proteins complexed with E7 protein of human papillomavirus." Although applicants believe that claim 1 as originally filed was enabled, it was in reliance on that statement by the Examiner and in the interests of furthering prosecution that applicants amended the claim in response to the first Office Action to limit the Hsp component of the fusion protein to an Hsp60 protein (or an immunostimulatory fragment thereof) and the HPV component of the fusion protein to an HPV E7 (or antigenic fragment thereof). In addition, claims 67-80 were added to require that both the Hsp60 component and the HPV E7 component of the fusion protein are full length proteins. Claims 70 and 71, respectively, require that the full length protein be *Mycobacterium bovis* BCG Hsp65 or type 16 HPV E7. However, in the present second Office Action the Examiner has acknowledged the enablement of none of the claims that were amended or added in response to the first Office Action.

The Examiner objected to claim 1 on the basis that "Hsp60" encompasses a "family" of molecules. According to the Examiner, "applicants have only observed full length HsP65 fused

to full length HPV-16 E7 protein" and "[e]xtrapolation from one fusion cannot be translated for any all whole host of molecules."

First, as detailed herein in response to the indefiniteness rejection, "Hsp60" proteins (which include mycobacterial Hsp65) constitute one of the major classes of Hsps and include proteins that are highly conserved in both their amino acid sequence and structure. It is because of the high degree of homology between Hsp60 proteins from different species that the skilled artisan at the time of filing of the present application would have reasonably expected that Hsp60 proteins, in addition to the particular Hsp60 protein *Mycobacterium bovis* BCG Hsp65, would work as a component of the fusion protein used in the claimed method.

Second, experiments using Hsp60 proteins other than *Mycobacterium bovis* BCG Hsp65 fused to an HPV E7 protein have confirmed that such fusion proteins are effective in eliciting a therapeutic anti-tumor immune response in an animal. As detailed in Siegel et al., U.S. Patent No. 6,495,347, fusion proteins containing either a *Streptococcus pneumoniae* Hsp65 or an *Aspergillus fumigatus* Hsp60 protein fused to an HPV type 16 E7 protein were injected into animals and shown to induce regression of a pre-established tumor expressing HPV16 E6/E7 (see column 22, line 20, to column 23, line 19; and column 25, line 60, to column 28, line 42). These experimental findings confirm that, as described in the present application, an "Hsp60" derived from different species can, like *Mycobacterium bovis* BCG Hsp65, be fused to an HPV E7 protein and be used to induce a therapeutic anti-HPV immune response in an animal.

The Examiner also asserted that it would require undue experimentation to carry out the claimed method using an "immunostimulatory fragment" of an Hsp60 protein and/or an "antigenic fragment" of an HPV E7 protein.

Fusion proteins containing fragments having the functional properties recited in the claims can, like fusion proteins containing full-length HPV E7 and/or Hsp60 proteins, be made by the skilled biologist without undue experimentation using recombinant techniques. In addition, fusion proteins containing fragments of an HPV E7 and/or an Hsp60 protein can be administered in the same way as a fusion protein containing only full-length proteins.

The effectiveness of a fusion protein containing a particular fragment of an Hsp60 and/or an HPV E7 protein can be determined by means of routine experimentation. The specification explains in detail a variety of exemplary assays that can be carried out to determine whether a given HPV component of a fusion protein can elicit a cross-reactive immune response (see page 12, line 25, to page 16 line 12). In addition, a fragment of an Hsp60 protein can also be readily evaluated to determine whether it constitutes an "immunostimulatory fragment." For example, a given fragment of an Hsp60 protein can be fused to an HPV type 16 E7 protein and tested in a mouse model system, e.g., a mouse injected with the TC-1 tumor cell line, to determine whether the fragment of the Hsp60 protein can elicit an appropriate immune response against an HPV protein in the mouse. The skilled artisan would understand that a fragment of an Hsp60 protein that, when fused to an HPV type 16 E7 protein, elicits a therapeutic immune response in the mouse constitutes an "immunostimulatory fragment" and can thus be effectively used in the claimed treatment method. Because assays to evaluate functional fragments of an Hsp60 protein and an HPV type 16 E7 protein involve only routine screening, the skilled biologist at the time of filing of the present application would have been able to carry out the full scope of the claimed method without undue experimentation.

35 U.S.C. § 112, 1st Paragraph (Written Description)

On pages 5-6 of the Office Action, the Examiner rejected claims 1-4, 6, 8-13, and 36-80 as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. According to the Examiner,

> [t]here is nothing in the specification that indicates applicants have taught or possessed the structures of the "fragments" of either "immunostimulatory fragment" or the "HPV E7" protein. Defining something by its "functional capability" is not the same as possession of that thing, this amounts to fishing exhibition [sic] and not full filing [sic] the written description. There is nothing in the disclosure that shows applicants have taught any fragment structure of the family of HsP60. Therefore, since applicants were not in possession of material that can be used in a method, as a consequence the written description of

invention is lacking.

Applicants respectfully traverse the rejection.

Claim 1 is directed to a method of treating a wart in a subject by administering to the subject a fusion protein containing an Hsp60 protein (or an immunostimulatory fragment thereof) and an HPV E7 protein (or an antigenic fragment thereof).

Claims 67-80 require that both the Hsp60 component as well as the HPV E7 component of the fusion protein be full length proteins. Accordingly, those sections of the Office Action asserting a lack of written description for claims to methods of using fragments of an Hsp60 and/or an HPV E7 protein do not apply to claims 67-80.

As detailed herein, an "immunostimulatory fragment" of an Hsp60 protein is a portion of an Hsp60 protein that, when contained in a fusion protein that also contains an HPV E7 protein or antigenic fragment thereof, facilitates an immune response to the HPV E7 protein or antigenic fragment thereof in a subject to whom the fusion protein is administered (see specification at page 4, line 29, to page 5, line 6). In addition, an "antigenic fragment" of an HPV E7 protein is a portion of an HPV E7 protein that, when contained in a fusion protein that also contains Hsp60 protein or immunostimulatory fragment thereof, elicits, in a subject to whom the fusion protein is administered, an immune response against the HPV E7 protein or the HPV E7 protein fragment (see specification at page 4, lines 18-28).

An immunostimulatory fragment of an Hsp60 protein is limited both by structure (the fragment constitutes a portion of an Hsp60 protein) as well as function (it must have an "immunostimulatory" activity, as that term is described herein). Similarly, an antigenic fragment of an HPV E7 protein is limited both by structure (the fragment constitutes a portion of an HPV E7 protein) as well as function (it must have an "antigenic" activity, as that term is described herein).

The claimed method does not encompass the use of *any* composition having a certain "functional capability." Rather, a composition used in the claimed method must contain all or part of the amino acid sequence of an Hsp60 protein and all or part of the amino acid sequence of an HPV E7 protein. This is an explicit structural requirement of the composition that is entirely

consistent with the disclosure contained in the application as filed. The amino acid sequence of Hsp60 proteins and HPV E7 proteins are well known to the skilled artisan. Accordingly, the skilled artisan can readily envision fragments of such proteins. In addition to a structural requirement, a fragment must have the specific functional property recited in the claim. Because of the requirement for both a particular structure and function, the fusion protein recited in the claimed methods claims is not described in terms of a desired result without structure, as was the case in *Regents of the University of California v. Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), a written description case cited by the Examiner in the first Office Action.

In light of the above, a person of ordinary skill in the art would clearly understand the structural/functional definition of the fusion protein recited in the claims and would therefore understand applicants to have been in possession of the claimed subject matter at the time the application was filed. Accordingly, applicants submit that the claims satisfy the written description requirement and request that the Examiner withdraw the rejection.

CONCLUSIONS

A Notice of Appeal and Petition for Three Month Extension of Time have already been filed.

Enclosed is a check for excess claims fees. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 12071-003001.

Respectfully submitted,

Date: December 4, 2003

Jack Brennan
Reg. No. 47,443

Fish & Richardson P.C.
45 Rockefeller Plaza, Suite 2800
New York, New York 10111
Telephone: (212) 765-5070
Facsimile: (212) 258-2291